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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,738	05/26/2000	Daniel A. Vallera	11983-004001	1069

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FISH & RICHARDSON P.C.
3300 DAIN RAUSCHER PLAZA
60 SOUTH SIXTH STREET
MINNEAPOLIS, MN 55402

EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/579,738	Applicant(s) VALLERA ET AL.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,12,15,17-25,34 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,15,17-25,34 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/9/03 has been entered.

Claims 1, 11, 34, 36, and 38 have been amended. Claims 10, 13, 14, and 26-33 have been canceled. Claims 1-9, 11, 12, 15, 17-25, 34, and 36-43 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #20 would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a subject with a hematopoietic or

metastatic cancer comprising intravenous or intraperitoneal administration of recited targeting T lymphocytes, does not reasonably provide enablement for treating any tumor by any route of administration of said targeting cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, claim 34 clearly state the intended use of the method as treating any tumor by any route of administration. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their

broadest reasonable interpretation that is consistent with the specification. Thus, the claim will be evaluated by the standard of a therapeutic method for treating cancer.

In view of the guidance provided, the specification teaches that the field of immunotoxin has been limited by an inability to escalate the does of immunotoxin administered to a subject to a level that is therapeutic but not unacceptably toxic, it shows by an in vitro assay that when the tumor specific CTLs secreting a cytokine (IL-4), the tumor killing power increased in tumors bearing IL-4 receptor compared to those not bearing IL-4 receptor (fig. 14), it teaches intravenous injection of tumor specific CTLs secreting IL-4/DT for treating subcutaneous injected myeloid leukemia cancer (fig. 15), whereby, the cancer volume is smaller in mice receiving the transduced CTLs. However, the specification and the declaration use tumor cells of hematopoietic origin, and injected into mice by subcutaneous or intraperitoneal, causing artificial tumor metastasis. The specification fails to teach whether the model is comparable to any tumor occurrence, particularly when the tumor is limited in an organ relatively isolated from circulation, such as those solid organ tumors recited in claim 12. The specification fails to teach whether the targeting cells could sufficiently reach the site of a target in a sufficient amount that would achieve a therapeutic effect, whether the targeting cells are sufficiently specific that they would not harm the innocent bystander cells when high amount of targeting cells is needed, and whether any route of administration such as intradermal and subcutaneous injection would achieve the same effect as intravenous and intraperitoneal

injection, thus, fails provide an enabling disclosure to support the full scope of the invention.

Turning to the state of the art, it is well known in the art that cell targeting is a significant barrier for successful immune therapy. For example, *Cochlovius et al* (Cancer Immunol Immunother 1998;46:61-6) teach, "THE ADOPTIVE TRANSFER OF *IN VITRO* GENERATED TUMOR-SPECIFIC CYTOTOXIC T LYMPHOCYTES IS CONSIDERED A PROMISING PERSPECTIVE IN CANCER THERAPY" (abstract), "THIS APPROACH ...HAS ONE MAJOR DRAWBACK. IN VITRO ACTIVATED LYMPHOCYTES DISPLAY ALTERED FEATURES OF HOMING UPON RETRANSPLANTION AND ARE FREQUENTLY TRAPPED IN THE SPLEEN AND THE LUNG" (1st paragraph, page 61). They go on to teach that adoptive transfer of CTLs could treat metastases but not the *local* tumor. They proposed to genetically modifying the CTLs to circumvent the drawback, but fail to provide any data to show that such approach is effective.

Thus, it is evident that at the time of the invention, the skilled artisan, while acknowledging the significant potential of genetically modifying the CTLs so that they could specifically target the tumor cells, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides data from an experimental model drawn to metastatic and hematopoietic tumors, it is not enabled for its full scope because the specification does not support the full scope of the claim.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* targeted immunotherapy using genetically modified T cells at therapeutic levels, in particular for the treatment of any and all tumors any where in the body using any mode of administration, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to treating localized tumors, and the breadth of the claims directed to a therapeutic effect, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11, 12, 15, 17, 18-25, 34, 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the pathogenic cell" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 34 is vague and indefinite because it does not recite a positive step that clearly relates back to the preamble.

Claim 36 recites the limitation, "said cell population of claim 22" in line 1, the limitation, "said cells" in line 4, 5, and 10. There is insufficient antecedent basis for this limitation in the claim.

Claim 38 recites the limitation "said DNA" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42, are rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), in view of *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80).

Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25 are drawn to a targeting cell (and cells) that is T lymphocyte transfected with a vector, preferably a retroviral vector; the vector comprising a nucleic acid sequence encoding a fusion protein, wherein the fusion protein comprising a targeting domain comprising a first member of an affinity pair that is not an antibody, and a toxic domain comprising a toxic

molecule; wherein the first member of the affinity pair is a cytokine, preferably IL-4, and the second member of the affinity pair is expressed on a surface of a cancer cell and is a cytokine receptor, such as IL-4 receptor. The vector further comprising transcriptional and translational regulatory sequences, and signal leader sequence allowing expression of said fusion protein in a cell of a mammal, wherein the T lymphocyte has significant binding affinity for a cancer cell, wherein the T lymphocyte is a CD8+ T lymphocyte, wherein the cancer cell is a malignant hematological cell, or a solid tissue cancer cell, and wherein the toxic domain is DT390 or PE. Claims 36 and 37 are drawn to a method of making the transfected T cells. Claims 38-42 are drawn to a viral vector comprising the mechanism for expressing said fusion protein in a mammalian cell.

Paul et al teach a retroviral vector encoding a chimeric (fusion) protein comprising a targeting domain, which vector could be used for directing gene delivery to a specific population of mammalian cells (abstract); wherein the vector comprising transcriptional control and regulation region (column 6, lines 64-67), wherein the targeting domain of the chimeric protein contains a ligand moiety capable of binding to receptors of the a target cell, such as cytokine IL-2 (column 6, line 1), and other native cytokine, muteins, and analog thereof (column 9, lines 45-60; column 10, lines 34-39), such as IL-4. *Paul et al* go on to teach that a preferred population of mammalian cells for targeted transfection is tumor-infiltrating lymphocytes (CD8+ lymphocytes having significant binding affinity for a cancer cell), hematopoietic cells, especially lymphocytes (column 26, lines 25-64), and when T cell suppression is desired, a toxin molecule could be included

in the construct (column 26, line 55). *Paul et al* also teach the transfection and enriching (selection) process (example 5). *Paul et al* do not make a cytokine-toxin expression construct.

Debinski et al teach that a wide range of human cancers expressing IL-4 receptors (2nd member of the affinity pair), e.g. T cell leukemia, breast cancer, prostate cancer and melanoma (table 1). They teach that such feature could be used for targeting toxins to the cancer cell (abstract). *Debinski et al* construct a plasmid vector comprising and expressing fusion protein of IL-4 and *Pseudomonas* exotoxin (PE, left column, page 14066). *Debinski et al* do not teach transfecting mammalian cells with the vector.

Chan et al teach targeting a diphtheria toxin, DT_{390} to cancerous hematopoietic cells using IL-3. They teach a plasmid vector comprising and expressing fusion protein of IL-3 and DT_{390}. *Chan et al* do not teach transfecting mammalian cells with the vector.

Chen et al teach that mammalian cells (leukemia lymphocytes) could be genetically modified to produce and secrete antibody targeted toxins using a retroviral vector having a signal sequence leading newly synthesized toxins into the lumen of ER, and the toxin-expressing cells remain viable (1st paragraph, page 78). *Chen et al* do not teach using a cytokine as a targeting domain.

Evidently, transducing mammalian cells such as T lymphocytes with a retroviral vector encoding a cytokine targeting domain and a toxin molecule is known in the art as taught by *Paul et al* and *Chen et al*, toxin-secreting mammalian cells could remain viable by including a leader sequence in the

vector construct is also known in the art as taught by *Chen et al*, and making a genetic construct comprising an cytokine targeting domain and a toxin molecule such as PE and DT390 is also well known in the art as taught by *Debinski et al, Chen et al,* and *Chan et al*. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al, Chan et al,* and *Chen et al*, by making a retroviral construct comprising a targeting domain and a toxin domain and using such for transducing T lymphocytes with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention as suggested by *Paul et al* when suppression or destruction of T lymphocytes are desired. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants are reminded that claim recitation, "targeting cell" has not given patentable weight in this and following rejection. This is because the recitation states the intended use of the cell composition. It is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand-alone. The MPEP states that,".. IN APPARATUS, ARTICLE, AND COMPOSITION CLAIMS, INTENDED USE MUST RESULT IN A STRUCTURAL DIFFERENCE BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART IN ORDER TO PATENTABLY DISTINGUISH THE CLAIMED INVENTION FROM THE PRIOR ART." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). In the instant case, the novelty of the claimed invention is determined by the structure of the vector and the type of cells transfected by the vector.

Claims 3 and 7 rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80), as applied to claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42above, and further in view of *Cochlovius et al* (Cancer Immunol Immunother 1998;46:61-6).

Claim 3 is drawn to a ligand for a cell adhesion receptor as the first member of the affinity pair, and claim 7 is drawn to the second member of the affinity pair is a cell adhesion receptor. The combined teachings of *Paul et al, Debinski et al, Chen et al*, and *Chan et al* fail to teach such a ligand.

However, before the effective filing date of instant application, *Cochlovius et al* teach a method for cancer therapy by administering (adoptive transfer) retrovirally transfected melanoma-specific cytotoxic T lymphocytes with a homing molecule CD44 (targeting domain), that is a ligand for haluronic acid on skin cell surface, so that the T lymphocytes would target the skin melanoma cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al,* and *Chen et al*, with that of *Cochlovius et al* by selecting a ligand that best suits their need in making the genetic construct with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention as done by *Cochlovius et al* for targeting T cells to the skin. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Paul et al* (US 5,736,387), *Chan et al* (J Blood 1996;88:1445-56), *Debinski et al* (J Bio Chem 1993;268:14065-70), and *Chen et al* (Nat 1997;385:78-80) as applied to claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42 above, and further in view of *Clay et al* (Pathol Oncol Res 1999 Jan;5:3-15) or *Buchsbaum et al* (US 6,001,329).

Claim 43 is drawn to a viral vector selected from the group consisting of adenoviral vector, AAV, vaccinia viral vector, and HSV. The combined teachings of *Paul et al, Debinski et al,* and *Chen et al*, fail to teach transducing T lymphocytes with these vectors.

However, before the effective filing date of instant application, *Clay et al* teach the pros and cons of various vector systems for transducing hematopoietic cells (table 3), particularly T lymphocytes (page 8, right column). *Buchsbaum et al* teach transducing T lymphocytes with adenoviral vectors (column 19-20).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Paul et al, Debinski et al,* and *Chen et al*, with that of *Clay et al* and *Buchsbaum et al* by selecting a viral vector that best suits their need in making the genetic construct with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention as suggested by *Clay et al.* Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

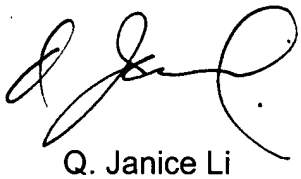
No claim is allowed. Claim 34 appears to be free of the cited prior art of record, however, it is subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
June 30, 2003